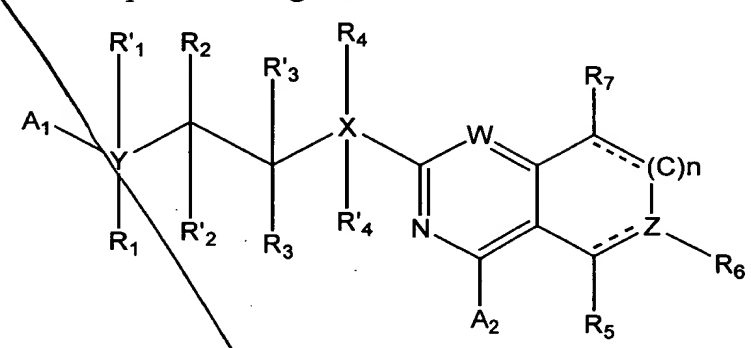
The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

That which is claimed is:

1. A compound having the structure:



(I)

wherein:

W and Z are optionally substituted carbon, nitrogen or sulfur;

X and Y are independently selected from the group consisting of nitrogen, oxygen, and optionally substituted carbon;

n is 0, 1 or 2;

A_1 and A_2 are optionally substituted aryl, aryloxy, arylamino or heteroaryl;

R_1, R_2, R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxyl, and optionally substituted loweralkyl, cyclooweralkyl, alkylaminoalkyl, loweralkoxy, amino, alkylamino, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteroaralkylcarbonyl, aryl and heteroaryl;

R'_1, R'_2, R'_3 and R'_4 are independently selected from the group consisting of hydrogen, and optionally substituted loweralkyl;

R_5, R_6 R_7 and are independently selected from the group consisting of hydrogen, hydroxy, halo, carboxyl, nitro, amino, amido, amidino, imido, cyano, and substituted or unsubstituted loweralkyl, loweralkoxy, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteraralkylcarbonyl, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkylaminocarbonyloxy, arylaminocarbonyloxy, formyl, loweralkylcarbonyl, loweralkoxycarbonyl, aminocarbonyl, aminoaryl, alkylsulfonyl, sulfonamido, aminoalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, alkylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, aralkylcarbonylamino, heteroaralkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, amidino, cycloalkyl, cycloamido, cyclothioamido, cycloamidino, heterocycloamidino,

cycloimido, heterocycloimido, guanidinyl, aryl, biaryl, heteroaryl, heterobiaryl, heterocyclo, heterocycloalkyl, arylsulfonyl and arylsulfonamido;

and the pharmaceutically acceptable salts thereof.

~~2. A compound of claim 1 wherein at least one of X and Y is nitrogen.~~

~~3.~~ A compound of claim 2 wherein one of X and Y is nitrogen and the other of X and Y is optionally substituted carbon.

~~4.~~ A compound of claim 2 wherein one of X and Y is nitrogen and the other of X and Y is oxygen.

~~5. A compound of claim 2, wherein both X and Y are nitrogen.~~

~~6.~~ A compound of claim 1, wherein at least one of A_1 and A_2 is an aromatic ring having from 3 to 10 carbon ring atoms and optionally 1 or more ring heteroatoms.

~~7.~~ A compound of claim ~~6~~, wherein at least one of A_1 and A_2 is optionally substituted carbocyclic aryl, arylamino or aryloxy.

~~8.~~ A compound of claim ~~6~~, wherein at least one of A_1 and A_2 is optionally substituted heteroaryl.

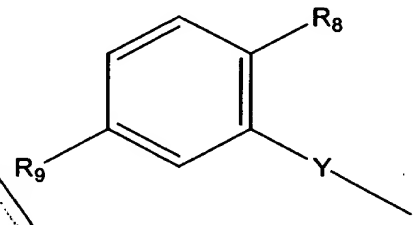
~~9.~~ A compound of claim ~~6~~, wherein at least one of A_1 and A_2 is selected from the group consisting of substituted or unsubstituted phenylamino and phenyloxy.

~~10.~~ A compound of claim ~~6~~, wherein at least one of A_1 and A_2 is selected from the group consisting of substituted or unsubstituted pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thiophenyl, furanyl, quinolinyl, purinyl, naphthyl, benzothiazolyl, benzopyridyl, and benzimidazolyl.

~~11.~~ A compound of claim ~~6~~, wherein at least one of A_1 and A_2 is substituted with at least one and not more than 3 substitution groups.

12. A compound of claim 11, wherein said substitution groups are independently selected from the group consisting of nitro, amino, cyano, halo, thioamido, amidino, oxamidino, alkoxyamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, loweralkyl, halologweralkyl, loweralkoxy, halologweralkoxy, loweralkoxyalkyl, loweralkylaminologweralkoxy, loweralkylcarbonyl, lowerarylalkylcarbonyl, lowerheteroarylalkylcarbonyl, alkylthio, aminoalkyl and cyanoalkyl.

13. A compound of claim 6 wherein at least one of A_1 and A_2 has the formula:



(II)

wherein Y is -NH or -O-; and

R_8 and R_9 are independently selected from the group consisting of hydrogen, nitro, amino, cyano, halo, thioamido, amidino, oxamidino, alkoxyamidino, imidino, guanidinyl, sulfonamido, carboxyl, formyl, loweralkyl, halologweralkyl, loweralkoxy, halologweralkoxy, loweralkoxyalkyl,loweralkylaminologweralkoxy, loweralkylcarbonyl, lowerarylalkylcarbonyl, lowerheteroarylalkylcarbonyl, alkylthio, aryl and, aralkyl.

14. A compound of claim 13, wherein A_1 and A_2 are selected from the group consisting of halo and halologweralkyl.

15. A compound of claim 14, wherein A_1 and A_2 are halo.

16. A compound of claim 13, wherein at least one of A_1 and A_2 is selected from the group consisting of 2,5-dichlorophenylamino and 2,5-dichlorophenyloxy.

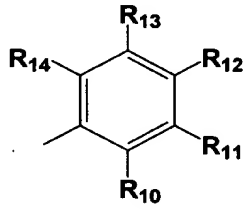
17. A compound of claim 1, wherein at least one of R_1, R_2, R_3 and R_4 is substituted loweralkyl selected from the group consisting of hydrogen, unsubstituted or substituted loweralkyl, halologweralkyl, heterocycloaminoalkyl, and loweralkylaminologweralkyl.

14 13
18. A compound of claim 17, wherein at least one of R_1, R_2, R_3 and R_4 is loweralkylaminoloweralkyl.

15 13
19. A compound of claim 17, wherein R_1, R_2, and R_3 are hydrogen and R_4 is selected from the group consisting of hydrogen, methyl, ethyl, aminoethyl, dimethylaminoethyl, pyridylethyl, piperidinyl, pyrrolidinylethyl, piperazinylethyl and morpholinylethyl.

16
20. A compound of claim 1, wherein at least one of R_5 and R_7 is selected from the group consisting of substituted and unsubstituted aryl, heteroaryl and biaryl.

17 16
21. A compound of claim 20 wherein at least one of R_5 and R_7 is a substituted or unsubstituted moiety of the formula:



(III)

wherein R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are independently selected from the group consisting of hydrogen, nitro, amino, cyano, halo, thioamido, carboxyl, hydroxy, and optionally substituted loweralkyl, loweralkoxy, loweralkoxyalkyl, halologweralkyl, halologweralkoxy, aminoalkyl, alkylamino, alkylthio, alkylcarbonylamino, aralkyl-carbonylamino, heteroaralkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino aminocarbonyl, loweralkylaminocarbonyl, aminoaralkyl, , loweralkylaminoalkyl, aryl, heteroaryl, cycloheteroalkyl, aralkyl, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, arylcarbonyloxyalkyl, alkylcarbonyloxyalkyl, heteroarylcarbonyloxyalkyl, aralkycarbonyloxyalkyl, and heteroaralkcarbonyl-oxyalkyl.

18 17
22. A compound of claim 21 wherein R_{10}, R_{11}, R_{13}, and R_{14} are hydrogen and R_{12} is selected from the group consisting of halo, loweralkyl, hydroxy, loweralkoxy, halologweralkyl, aminocarbonyl, alkylaminocarbonyl and cyano.

19 17
23. A compound of claim 21 wherein R_{11}, R_{13}, and R_{14} are hydrogen and R_{10} and R_{12} are independently selected from the group consisting of halo, loweralkyl, hydroxy, loweralkoxy, haloloweralkyl and cyano.

20 17
24. A compound of claim 21 wherein R_{10}, R_{11}, R_{13}, and R_{14} are hydrogen and R_{12} is heteroaryl.

21 17
25. A compound of claim 21 wherein R_{10}, R_{11}, R_{13}, and R_{14} are hydrogen and R_{12} is a heterocycloalkyl.

5 of 7

22 17
26. A compound of claim 21 wherein at least one of R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are halo and the remainder of R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are hydrogen.

23 17
27. A compound of claim 21 wherein at least one of R_5 and R_7 is selected from the group consisting of dichlorophenyl, difluorophenyl, trifluoromethylphenyl, chlorofluorophenyl, bromochlorophenyl, ethylphenyl, methylchlorophenyl, imidazolylphenyl, cyanophenyl, morphlinophenyl and cyanochlorophenyl.

24
28. A compound of claim 1, wherein R_6 is substituted alkyl selected from the group consisting of aralkyl, hydroxyalkyl, aminoalkyl, aminoaralkyl, carbonylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, aralkylcarbonylaminoalkyl, aminoalkoxyalkyl and arylaminoalkyl.

25
29. A compound of claim 1, wherein R_6 is substituted amino selected from the group consisting of alkylamino, alkylcarbonylamino, alkoxycarbonylamino, arylalkylamino, arylcarbonylamino, alkylthiocarbonylamino, arylsulfonylamino, heteroarylamino alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, aralkylcarbonylamino, and heteroaralkylcarbonylamino.

26
30. A compound of claim 1, wherein R_6 is selected from the group consisting of unsubstituted or substituted aminocarbonyl, alkyloxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl and alkylaminoalkyloxycarbonyl.

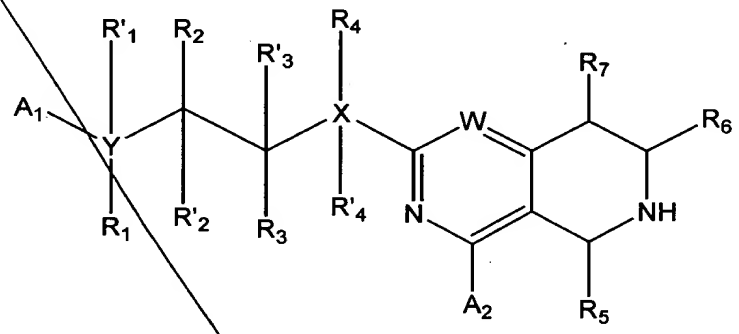
27
31. A compound of claim 1, wherein R_6 is selected from the group consisting of amidino, guanidino, cycloimido, heterocycloimido, cycloamido, heterocycloamido, cyclothioamido and heterocyclooloweralkyl.

28
32. A compound of claim 1, wherein R_6 is aryl.

29
33. A compound of claim 1, wherein R_6 is heteroaryl.

30 29
34. A compound of claim 33, wherein R_6 is selected from the group consisting of substituted or unsubstituted pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thienyl, furanyl, quinolinyl, pyrrolylpyridyl, benzothiazolyl, benzopyridyl, benzotriazolyl, and benzimidazolyl.

35. A compound having the structure:



(I)

wherein:

W is optionally substituted carbon, nitrogen or sulfur;

X and Y are independently selected from the group consisting of nitrogen, oxygen, and optionally substituted carbon;

A_1 and A_2 are optionally substituted aryl, aryloxy, arylamino or heteroaryl;

R_1, R_2, R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxyl, and optionally substituted loweralkyl, cycloloweralkyl, alkylaminoalkyl, loweralkoxy, amino, alkylamino, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteroaralkylcarbonyl, aryl and heteroaryl;

R'_1, R'_2, R'_3 and R'_4 are independently selected from the group consisting of hydrogen, and optionally substituted loweralkyl;

R_5, R_6 R_7 and are independently selected from the group consisting of hydrogen, hydroxy, halo, carboxyl, nitro, amino, amido, amidino, imido, cyano, and substituted or unsubstituted loweralkyl, loweralkoxy, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteraralkylcarbonyl, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, alkylaminocarbonyloxy, arylaminocarbonyloxy, formyl, loweralkylcarbonyl, loweralkoxycarbonyl,

aminocarbonyl, aminoaryl, alkylsulfonyl, sulfonamido, aminoalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroaralkylamino, alkylcarbonylamino, alkylaminocarbonylamino, arylaminocarbonylamino, aralkylcarbonylamino, heteroaralkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, amidino, cycloalkyl, cycloamido, cyclothioamido, cycloamidino, heterocycloamidino, cycloimido, heterocycloimido, guanidinyl, aryl, biaryl, heteroaryl, heterobiaryl, heterocyclo, heterocycloalkyl, arylsulfonyl and arylsulfonamido;

and the pharmaceutically acceptable salts thereof.

~~36. A compound of claim 35 wherein at least one of X and Y is~~ nitrogen.

~~37.~~ A compound of claim 36 wherein one of X and Y is nitrogen and the other of X and Y is optionally substituted carbon.

~~38.~~ A compound of claim 36 wherein one of X and Y is nitrogen and the other of X and Y is oxygen.

~~39. A compound of claim 36, wherein both X and Y are nitrogen.~~

~~40~~. A compound of claim ~~35~~, wherein at least one of A_1 and A_2 is an aromatic ring having from 3 to 10 carbon ring atoms and optionally 1 or more ring heteroatoms.

~~41.~~ A compound of claim ~~40~~, wherein at least one of A_1 and A_2 is optionally substituted carbocyclic aryl, arylamino or aryloxy.

~~42.~~ A compound of claim ~~40~~, wherein at least one of A_1 and A_2 is optionally substituted heteroaryl.

~~43.~~ A compound of claim ~~40~~, wherein at least one of A_1 and A_2 is selected from the group consisting of substituted or unsubstituted phenylamino and phenyloxy.

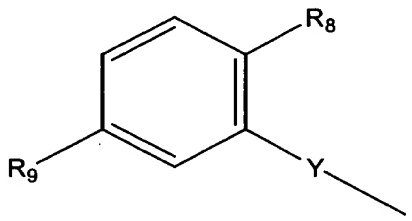
~~44.~~ A compound of claim ~~40~~, wherein at least one of A_1 and A_2 is selected from the group consisting of substituted or unsubstituted pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl,

triazolyl, thiophenyl, furanyl, quinolinyl, purinyl, naphthyl, benzothiazolyl, benzopyridyl, and benzimidazolyl.

~~45~~ 37. A compound of claim ~~40~~ 32, wherein at least one of A_1 and A_2 is substituted with at least one and not more than 3 substitution groups.

~~46~~ 38. A compound of claim ~~45~~ 37, wherein said substitution groups are independently selected from the group consisting of nitro, amino, cyano, halo, thioamido, amidino, oxamidino, alkoxyamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, loweralkyl, haloloweralkyl, loweralkoxy, haloloweralkoxy, loweralkoxyalkyl, loweralkylaminoloweralkoxy, loweralkylcarbonyl, loweraralkylcarbonyl, lowerheteroaralkylcarbonyl, alkylthio, aminoalkyl and cyanoalkyl.

~~47~~ 39. A compound of claim ~~40~~ 32 wherein at least one of A_1 and A_2 has the formula:



(II)

wherein Y is -NH or -O-; and

R_8 and R_9 are independently selected from the group consisting of hydrogen, nitro, amino, cyano, halo, thioamido, amidino, oxamidino, alkoxyamidino, imidino, guanidinyl, sulfonamido, carboxyl, formyl, loweralkyl, haloloweralkyl, loweralkoxy, haloloweralkoxy, loweralkoxyalkyl,loweralkylaminoloweralkoxy, loweralkylcarbonyl, loweraralkylcarbonyl, lowerheteroaralkylcarbonyl, alkylthio, aryl and, aralkyl.

~~48~~ 40. A compound of claim ~~47~~ 39, wherein A_1 and A_2 are selected from the group consisting of halo and halooweralkyl.

~~49~~ 41. A compound of claim ~~48~~ 40, wherein A_1 and A_2 are halo.

~~50~~ 42. A compound of claim ~~47~~ 39, wherein at least one of A_1 and A_2 is selected from the group consisting of 2,5-dichlorophenylamino and 2,5-dichlorophenyloxy.

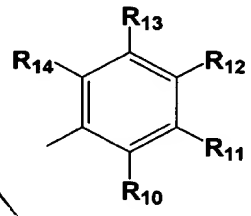
51. A compound of claim 35, wherein at least one of R_1, R_2, R_3 and R_4 is substituted loweralkyl selected from the group consisting of hydrogen, unsubstituted or substituted loweralkyl, halologweralkyl, heterocycloaminoalkyl, and loweralkylaminoloweralkyl.

52. A compound of claim 51, wherein at least one of R_1, R_2, R_3 and R_4 is loweralkylaminoloweralkyl.

53. A compound of claim 51, wherein R_1, R_2, and R_3 are hydrogen and R_4 is selected from the group consisting of hydrogen, methyl, ethyl, aminoethyl, dimethylaminoethyl, pyridylethyl, piperidinyl, pyrrolidinylethyl, piperazinylethyl and morpholinylethyl.

54. A compound of claim 35, wherein at least one of R_5 and R_7 is selected from the group consisting of substituted and unsubstituted aryl, heteroaryl and biaryl.

55. A compound of claim 54 wherein at least one of R_5 and R_7 is a substituted or unsubstituted moiety of the formula:



(III)

wherein R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are independently selected from the group consisting of hydrogen, nitro, amino, cyano, halo, thioamido, carboxyl, hydroxy, and optionally substituted loweralkyl, loweralkoxy, loweralkoxyalkyl, halologweralkyl, halologweralkoxy, aminoalkyl, alkylamino, alkylthio, alkylcarbonylamino, aralkyl-carbonylamino, heteroaralkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino aminocarbonyl, loweralkylaminocarbonyl, aminoaralkyl, , loweralkylaminoalkyl, aryl, heteroaryl, cycloheteroalkyl, aralkyl, alkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, arylcarbonyloxyalkyl, alkylcarbonyloxyalkyl, heteroarylcarbonyloxyalkyl, aralkycarbonyloxyalkyl, and heteroaralkcarbonyl-oxyalkyl.

48 47

56. A compound of claim 55 wherein R_{10}, R_{11}, R_{13}, and R_{14} are hydrogen and R_{12} is selected from the group consisting of halo, loweralkyl, hydroxy, loweralkoxy, haloloweralkyl, aminocarbonyl, alkylaminocarbonyl and cyano.

49 47

57. A compound of claim 55 wherein R_{11}, R_{13}, and R_{14} are hydrogen and R_{10} and R_{12} are independently selected from the group consisting of halo, loweralkyl, hydroxy, loweralkoxy, haloloweralkyl and cyano.

Sub D13

50 47

58. A compound of claim 55 wherein R_{10}, R_{11}, R_{13}, and R_{14} are hydrogen and R_{12} is heteroaryl.

51 47

59. A compound of claim 55 wherein R_{10}, R_{11}, R_{13}, and R_{14} are hydrogen and R_{12} is a heterocycloalkyl.

52 47

60. A compound of claim 55 wherein at least one of R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are halo and the remainder of R_{10}, R_{11}, R_{12}, R_{13}, and R_{14} are hydrogen.

53 47

61. A compound of claim 55 wherein at least one of R_5 and R_7 is selected from the group consisting of dichlorophenyl, difluorophenyl, trifluoromethylphenyl, chlorofluorophenyl, bromochlorophenyl, ethylphenyl, methylchlorophenyl, imidazolylphenyl, cyanophenyl, morphlinophenyl and cyanochlorophenyl.

54 31

62. A compound of claim 33, wherein R_6 is substituted alkyl selected from the group consisting of aralkyl, hydroxyalkyl, aminoalkyl, aminoaralkyl, carbonylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, aralkylcarbonylaminoalkyl, aminoalkoxyalkyl and arylaminoalkyl.

55 31

63. A compound of claim 33, wherein R_6 is substituted amino selected from the group consisting of alkylamino, alkylcarbonylamino, alkoxycarbonylamino, arylalkylamino, arylcarbonylamino, alkylthiocarbonylamino, arylsulfonylamino, heteroarylamino alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, aralkylcarbonylamino, and heteroaralkylcarbonylamino.

56 31

64. A compound of claim 33, wherein R_6 is selected from the group consisting of unsubstituted or substituted aminocarbonyl, alkyloxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl and alkylaminoalkyloxycarbonyl.

57 31
~~65.~~ A compound of claim ~~35~~, wherein R_6 is selected from the group consisting of amidino, guanidino, cycloimido, heterocycloimido, cycloamido, heterocycloamido, cyclothioamido and heterocyclololoweralkyl.

58 31
~~66.~~ A compound of claim ~~35~~, wherein R_6 is aryl.

59 31
~~67.~~ A compound of claim ~~35~~, wherein R_6 is heteroaryl.

60 59
~~68.~~ A compound of claim ~~67~~, wherein R_6 is selected from the group consisting of substituted or unsubstituted pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thienyl, furanyl, quinolinyl, pyrrolylpyridyl, benzothiazolyl, benzopyridyl, benzotriazolyl, and benzimidazolyl.

69. A composition comprising an amount of a compound of claim 1 effective to modulate GSK3 activity in a human or animal subject when administered thereto, together with a pharmaceutically acceptable carrier.

62
~~70.~~ A method of inhibiting GSK3 activity in a human or animal subject, comprising administering to the human or animal subject a composition of claim ~~69~~. 61

63
~~71.~~ A method of treating a cell comprising administering to the cell an amount of a compound of claim 1 effective to inhibit GSK3 activity in the cell.

72. A method for treating a GSK3-mediated disorder in a human or animal subject, comprising administering to the human or animal subject an amount of a composition of claim 69 effective to inhibit GSK3 activity in the subject.

65 64
~~73.~~ A method of claim ~~72~~, wherein the composition is administered by a mode of administration selected from the group consisting of oral, subcutaneous, transdermal, transmucosal, iontophoretic, intravenous, intrathecal, buccal, sublingual, intranasal, and rectal administration.

66 64
~~74.~~ A method of claim ~~72~~, wherein said GSK3-mediated disorder is selected from the group consisting of diabetes, ~~Alzheimer's disease,~~ obesity, atherosclerotic cardiovascular disease, essential hypertension, polycystic ovary

Sub D1

syndrome, syndrome X, ischemia, traumatic brain injury, bipolar disorder, immunodeficiency and cancer.

75. A method of claim 74, which further comprises administering to the subject one or more additional active agents.

76. A method of claim 75, wherein the GSK3-mediated disorder is diabetes and the additional active agent is selected from the group consisting of insulin, troglitazone, rosiglitazone, pioglitazone, glipizide and metformin.

77. A compound of claim 1 for use as a pharmaceutical.

78. Use of a compound of claim 1 in the manufacture of a medicament for the treatment of diabetes, Alzheimer's disease and other neurodegenerative disorders, obesity, atherosclerotic cardiovascular disease, essential hypertension, polycystic ovary syndrome, syndrome X, ischemia, traumatic brain injury, bipolar disorder or cancer.